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Randomized Comparison of Moderate-Dose Methotrexate Infusions to Oral Methotrexate in Children With Intermediate Risk Acute Lymphoblastic Leukemia: A Childrens Cancer Group Study

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Methotrexate (MTX) infusions of 500–1,000 mg/m^2 over 24 hours may improve survival and prevent relapse in children with acute lymphoblastic leukemia (ALL). Childrens Cancer Group (CCG) Study 139 compared weekly oral methotrexate 20 mg/m^2/week (oral MTX) to MTX 500 mg/m^2 infused over 24 hours (IV MTX) three times during consolidation and every 6 weeks during maintenance in 164 children with intermediate-risk ALL, i.e., those patients over age 1 year with white blood cell count 10,000 to 49,999/ml and no bulky extramedullary disease. Median follow-up for CCG-139 exceeded 75 months.

Thirty-four events occurred among 80 patients receiving IV and oral MTX and 36 events among 84 patients receiving oral MTX. Two children died during induction and one did not enter remission. Remission induction rate is 98%. There have been 26 marrow relapses, 11 combined marrow and extramedullary relapses, 24 CNS relapses, and five testicular or other relapses. The frequency and distribution of relapses does not differ between the two regimens. For the entire group, overall event-free survival (EFS) at 6 years is 57.9% (standard deviation =4.0%) and actuarial survival is 80.0% (standard deviation =3.3%). Of the 29 patients with isolated extramedullary relapse, 18 survive free of a second event, a median of 42 months from relapse. In contrast to other trials, this trial does not show that IV MTX in this dose and schedule offers an advantage over standard therapy for this group of children.

Key words: acute lymphoblastic leukemia, methotrexate, intermediate risk ALL

INTRODUCTION

Standard therapy for children with acute lymphoblastic leukemia (ALL) has consisted of an induction phase, a central nervous system consolidation phase, and a maintenance phase lasting 2 to 5 years [1–7]. From 1970 to 1988 in the clinical trials of the Childrens Cancer Group (CCG) and others, drugs used in standard induction were vincristine, prednisone, L-asparaginase, and intrathecal methotrexate. Consolidation involved daily oral 6-mercaptopurine and intrathecal methotrexate with or without cranial irradiation, while standard maintenance included oral methotrexate and 6-mercaptopurine with monthly pulses of vincristine and prednisone and intrathecal therapy trimonthly. Patients could be stratified into three risk groups based on age, gender, white blood cell count, and French/American/British (FAB) morphology [4,8]. Standard therapy achieved cure in over half the children with low-risk ALL or with intermediate-risk ALL, i.e., those over age 1 year with white blood cell count (WBC) 10,000 to <50,000 and without bulky extramedullary disease or with WBC <10,000 and FAB L2 morphology [2–7].

Between 1970 and 1980, CCG and others manipulated doses and schedules of the drugs used in standard therapy and introduced anthracyclines, alkylating agents, and cytosine arabinoside in the various phases of therapy. Among the many randomized trials and uncontrolled trials of this decade, only two strategies stood out: 1) the Berlin-Frankfurt-Münster (BFM) intensification regimen and 2) 24-hour infusions of moderately high-dose methotrexate [9]. In 1983, CCG began a series of randomized

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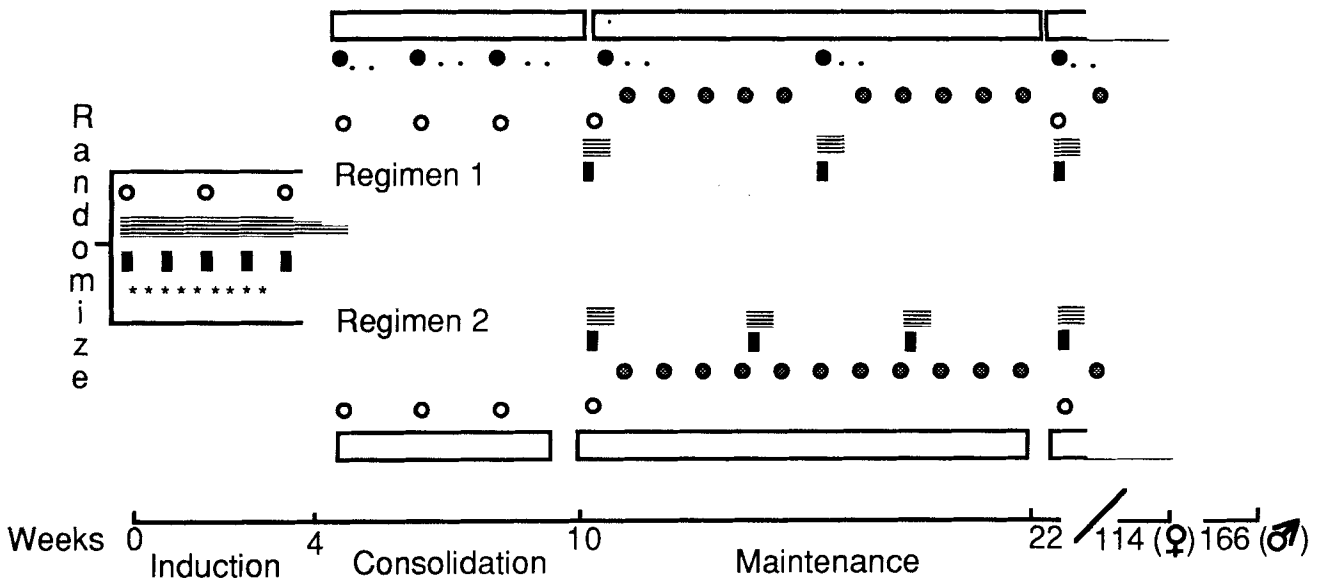

Fig. 1. CCG-139 treatment schema. *, L-asparaginase, 6,000 U/m2 IM; ▮, Vincristine 1.5 mg/m2 IV; ≣, Prednisone 40 mg/m2; □, 6-Mercaptopurine 75 mg/m2/day; ○, Methotrexate 8, 10, or 12 mg IT; ●, Methotrexate 20 mg/m2 po q week; ●, Methotrexate 500 mg/m2 IV infusion; •, Leukovorin 12 mg/m2.

trials to confirm and extend the experience with these two approaches in children with intermediate-risk ALL. The major group-wide study, CCG-105, compared standard therapy to the BFM therapy or parts of the BFM therapy. Two concurrent limited-institution randomized trials evaluated infusional methotrexate: CCG-144 tested methotrexate infusions of 33 g/m^2; CCG-139 compared standard oral methotrexate to methotrexate infusions of 500 mg/m^2 three times during consolidation and every 6 weeks during maintenance. This report describes the results of CCG-139 with a median follow-up of 75 months. Participating institutions were Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Cooper Medical Center, Geisinger Medical Center, and A.I. Dupont Medical Center.

PATIENTS AND METHODS

Diagnosis of ALL was made on smears of marrow aspirates stained with Wrights-Giemsa, periodic acid Schiff, peroxidase, Sudan Black, acid phosphatase, and α naphthyl-acetate esterase with and without fluoride inhibition. FAB morphology was determined at the primary institution and reviewed at the CCG leukemia morphology reference laboratory [8].

The CCG definition of intermediate-risk ALL was as follows: age >1 and <19 years; no bulky lymphomatous disease; white blood cell count 10,000–49,999/μl or WBC <10,000 and >10% blasts with L_2 morphology. All eligible patients at participating institutions were entered on CCG-139.

Figure 1 illustrates the two treatment regimens. Induction and CNS prophylaxis were identical for the two regimens. Regimen 1 included infusions of methotrexate at 500 mg/m^2 with ⅓ as bolus and ⅔ as a 24-hour infusion three times during consolidation and every 6 weeks during maintenance. Methotrexate was followed by leukovorin factor at 48 and 72 hours. Weekly oral methotrexate at 20 mg/m^2 was given during the 5 weeks in which there was no IV methotrexate. In Regimen 1 vincristine/prednisone pulses were given every 6 weeks. In Regimen 2, patients received standard oral methotrexate 20 mg/m^2 once each week and vincristine/prednisone pulses every 4 weeks. Treatment continued for 2 years from the end of consolidation for girls and 3 years for boys [2]. For girls, the calculated cumulative dose of oral plus intravenous methotrexate was 11,749 mg/m^2 in Regimen 1 and 2,080 mg/m^2 in Regimen 2; for boys Regimen cumulative systemic methotrexate was 16,240 mg/m^2 in Regimen 1 and 3,120 mg/m^2 in Regimen 2. Thirty patients received their maintenance infusion methotrexate at home [10]. The protocol was approved by the Institutional Review Boards of participating hospitals.

STATISTICS

This study initially began at one institution (Philadelphia) and was then expanded to include four additional institutions. At that time, the study was officially designated as a limited institution study of the CCG. Based on previous CCG studies, the projected 3-year and 5-year event-free survival (EFS) were 66% and 55%, respec-

tively, for intermediate-risk patients treated with standard therapy. The study accrued 164 patients which provides power of 75% for detecting a change in the long-term EFS from 60 to 80% (Type I error =0.05, two-sided test). Endpoints in this study included attainment of remission, EFS, bone marrow relapse, and survival. Life-table curves were based on Kaplan-Meier estimate and comparison of groups used the log-rank statistic [11–13]. The standard deviation of the life table estimate was obtained by Greenwood's formula. An approximate 95% confidence interval can be obtained by using the life table estimate ±1.96 standard deviations. The life table estimated relative event rate was calculated by the o/e method. The first 16 patients were non-randomly assigned therapy in a feasibility pilot: patients 1 to 6 were assigned the standard arm; patients 7 to 16 received the investigational regimen; patients 17 through 44 were randomly assigned treatment (in Philadelphia) with stratification for white blood cell count and gender. Thereafter, all randomizations took place in the CCG Operations Office. This report includes all 164 eligible patients including the first 16 who were non-randomly entered. Analyses using only the group of 148 randomized patients gives very similar results.

RESULTS

Between 11/15/84 and 1/15/89, 168 patients were entered on CCG-139; 164 were eligible. Table I lists the demographic features of the patient population. Although there are no significant differences between the two groups, a higher proportion of patients in Regimen 1 were over age 10 years, an age which has subsequently been considered high risk. Three patients were removed from Regimen 1 because of parent or physician preference and one was removed because of CNS toxicity. These patients continued in follow-up for major disease endpoints and survival. Five patients in continuous remission (CCR) have been lost to follow-up (LTFU) between 3½ and 5½ years from diagnosis. They are censored from time last seen. Comparison of regimens in the following analysis is based on "intent to treat," i.e., the regimen originally assigned.

Table II lists events. There were 34 events among 80 patients receiving Regimen 1 and 36 events among 84 patients on Regimen 2. Two children died before entering remission and one did not enter remission. Remission induction rate is 98%. There have been 26 marrow relapses, 10 combined marrow and extramedullary relapses, 24 isolated CNS relapses, four isolated testicular, one testicular/CNS, and one other extramedullary relapse. The frequency and distribution of relapses does not differ between the two regimens and are similar to those of intermediate-risk patients receiving standard therapy in past and concurrent CCG studies.

TABLE I. CCG-139 Patient Demographics

	Regimen 1 IV MTX	Regimen 2 Standard
Number	80	84
Age (yr)		
<10	55	69
>10	25	15
Gender (n)		
Male	42	46
Female	38	38
WBC/μl (n)		
<10,000[a]	41	38
10–20,000	19	21
20–49,999	20	25
LTFU[a]	3	2
Off study[b]	4	0

[a]LTFU—five patients were lost-to follow-up in CCR at 3.5, 4, 5, 5.5, and 5.5 years.
[b]One patient removed from study because of CNS toxicity; three were removed because of physician or patient choice.

TABLE II. CCG-139 Events

	Regimen 2 (n)	Regimen 2 (n)
Induction failure	0	1
Early deaths	1	2
Relapses		
Marrow	12	14
Combined relapses		
Marrow/CNS	4	5
Marrow/testis	0	1
Extramedullary		
CNS	14	10
Testis	2	2
CNS/testis	1	0
Other	0	1
Total relapses	33	33
Total events	34	36

The actuarial event-free survival at 6 years is 57.4% (±5.6) in the standard group and 58.4% (±5.6) in the experimental group ($P = 0.92$) (Fig. 2). The relative event rate is 1.02 for the experimental group compared to the standard group. There have been 14 and 19 deaths on the two regimens. Life table estimates survival at 6 years is 83.1 (±4.3) and 76.9% (±5.0) (Fig. 3), respectively ($P = 0.31$), with an estimated relative death rate of 1.43. Among the 29 patients with isolated extramedullary relapse, 19 (65%) survive event-free at a median of 42 months (11–103 months) from relapse. In additional analyses, age, gender, WBC, and FAB morphology did not emerge as significant risk factors for the population as a whole or for either treatment group.

Hematologic toxicities during induction and consolidation were no different in the two regimens. Transient elevations of transaminases occurred consistently in patients receiving Regimen 1. One patient discontinued Regimen 1 because of encephalopathy that became pro-

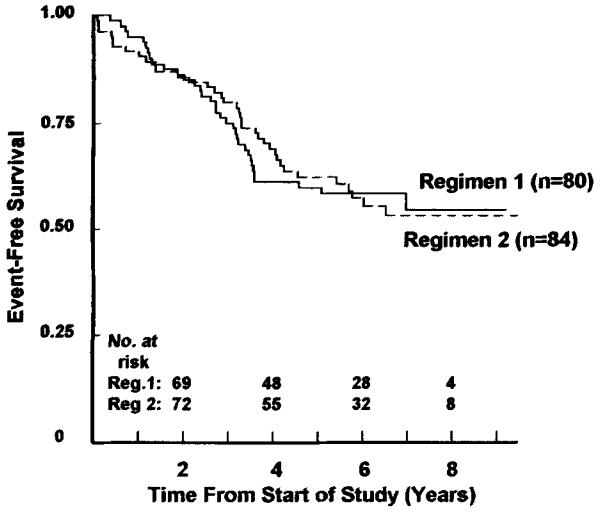

Fig. 2. Kaplan-Meier estimate of the actuarial event-free survival in Regimens 1 and 2 from the time on study.

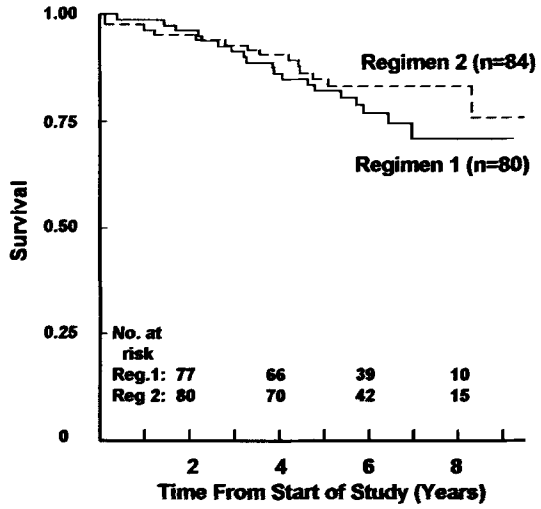

Fig. 3. Kaplan-Meier estimate of the actuarial survival in Regimens 1 and 2 from the time on study.

gressively severe following each course of intravenous methotrexate. Three fatal complications occurred: 1) death from aortic rupture and hemorrhage caused by disseminated aspergillosis during induction (Regimen 2); 2) death from presumed sepsis during induction (Regimen 2); and 3) death from varicella with encephalitis during maintenance (Regimen 1).

DISCUSSION

There is wide interpatient and intrapatient variation in absorption, pharmacokinetics, and bioavailability of oral methotrexate and 6-mercaptopurine, the mainstays of maintenance therapy in ALL [14–16]. This variation accounts for the failure of some patients with intermediate risk ALL to sustain a remission. In theory, using doses higher than the standard weekly 20 to 40 mg/m^2 and parenteral administration of methotrexate or 6-mercaptopurine addresses the problem of absorption and bioavailability and may solve some problems with compliance and tolerance [14–17].

In fact, high-dose intensity and parenteral administration of methotrexate have been shown to improve outcome [8,15,16,18–23]. Single regimen, non-randomized trials of parenteral moderate-dose methotrexate suggested that parenteral drug not only reduced marrow relapse rate, but also prevented extramedullary relapses and obviated the need for prophylactic cranial irradiation [9,19,21–23]. The randomized trial of Freeman et al. confirmed the reduction in marrow relapse rate: at a median follow-up of 40 months, 9 of 117 intermediate-risk patients given 500 mg/m^2 of infusion methotrexate three times during consolidation experienced marrow relapses compared to 24 of 120 given standard oral methotrexate and cranial irradiation ($P < 0.01$) [18]. The CNS relapse rate was significantly higher in the infusion methotrexate group ($P = 0.01$). The early single arm studies and that of Freeman prompted CCG-139. Subsequently, St. Jude Children's Research Hospital's Total X Study has demonstrated that infusions of methotrexate 1,000 mg/m^2 given three times during consolidation and every 6 weeks in maintenance conferred a higher event-free survival than standard consolidation with cranial irradiation and maintenance with oral 6-mercaptopurine and methotrexate plus pulses of doxorubicin, cyclophosphamide, teniposide, and cytarabine [24]. Neither Chessels et al. nor the Medical Research Council Working Party (MRC) were able to demonstrate any benefit to weekly intramuscular methotrexate given at the standard 20 mg/m^2 dose, but the MRC did find that the parenteral route was more neurotoxic among patients who had also received prophylactic cranial irradiation [25].

The results of CCG-139 do not show any benefit to infusion methotrexate. The study does not support the hypotheses that the parenteral route and higher doses will improve outcome by overcoming poor absorption or limited bioavailability. In its use of 500 mg/m^2 over 24 hours, CCG-139 closely resembles the Acute Leukemia Group B (ALGB) study of Freeman et al. [18], but the cumulative dose of methotrexate is much higher in CCG-139. Evans et al. documented considerable variation in methotrexate levels among children receiving a 24-hour infusion of 1,000 mg/m^2 of methotrexate and these variations had an impact on response: those with mean levels of methotrexate <16 mm had a seven-fold higher risk of marrow relapse than those whose level was >16 mm [15]. Conceivably, the use of 1 g/m^2 rather than 0.5 g/m^2 brought a greater number of the St. Jude patients into the therapeutic range. On the other hand, Pearson et al. have not found that high serum concentration and area under

the plasma concentration curve were associated with a lower relapse rate [16].

It is not possible to reconcile our data with those of similar randomized trials. This study is smaller than St. Jude Study X and the ALGB study of Freeman et al. [18,24]. It does not have great power to prove equality between the regimens. However, if a difference exists, it is of the order of 7 or 8%. Moreover, this study shows no trend for superiority of the IV methotrexate regimen. Subtle variations in the definition of intermediate-risk patients and in induction and maintenance programs may account for the differences in outcome among these studies. In CCG-139, patients randomized to infusion methotrexate received about ⅓ less vincristine and prednisone during maintenance, possibly obscuring the beneficial effect of the methotrexate. When CCG-139 was designed, there was evidence from St. Jude Children's Research Hospital and from early results of CCG-161 that vincristine/prednisone pulses conferred no benefit [5,26]. More mature results of CCG-161 showed the monthly vincristine and prednisone pulses conferred a lower relapse rate in low-risk patients when compared to no pulses. It is not possible to know whether the reduced number of vincristine pulses in CCG-139 had any impact on the outcome [5]. However, no pulses were given with infusion methotrexate in the Total X therapy [24].

Although the results of this study raise a number of questions, they may not be worthy of further investigation in this group of patients. Since the completion of this study, at least three other strategies have emerged that may be superior to the infusion methotrexate protocols: the Dana Farber four- drug induction, followed by consolidation utilizing repetitive high-dose L-asparaginase; the combined use of infusion methotrexate and 6-mercaptopurine; and the CCG-105 modification of the original BFM protocol which includes only the delayed intensification component of the original BFM therapy [27–29]. Among children <10 years of age, the CCG-105 study achieved a 5-year event-free survival of $80 \pm 3\%$ with the relatively simple addition of BFM delayed intensification 4 months after diagnosis and without the use of cranial irradiation [30,31]. As BFM delayed intensification is associated with relatively low risk of serious acute and delayed complications, CCG successfully adopted BFM delayed intensification as standard therapy for this group of patients [27,30,31]. At this time CCG has abandoned the studies of parenteral methotrexate in favor of investigating modification of delayed intensification with the goal of approaching a 90% 5-year event-free survival for the group of children with intermediate-risk ALL.

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